Applicants respectfully request that the Examiner give consideration to examining all inventions of the present application set forth in claims 53-91 because there is unity of invention, or alternatively, groups I-XXX inasmuch as the Examiner indicates that each of the inventions are classified *in the same class and subclasses*, namely, class 424, subclass 520. Because these inventions may be found and searched in the same class and subclasses, it is respectfully submitted that the Examiner may efficiently and without undue burden, examine all of the inventions set forth in groups I-XXX. Thus, the construction that Applicants posit in requesting the Examiner examine the inventions of claims 53-91, or alternatively, the invention of groups I-XXX , is in compliance with the policy behind MPEP 803.

The Examiner has posited a number of reasons for the restriction requirement. Applicants respectfully submit that the stated reasons are simply not cogent and Applicants request withdrawal of the restriction requirement entirely *or at least* limit the restriction to the inventions of claims 53-91 or alternatively, groups I-XXX, as indicated above. The Examiner indicates, *inter alia,* that restriction is warranted because the inventions listed as Groups I-XLII do not relate to a single inventive concept under PCT Rule 13.1, because, under PCT Rule 13.2, the inventions lack the same or corresponding technical features for the stated reasons. Applicants respectfully disagree. Applicants address each of the Examiner's suppositions and set forth the reasons for their traversal in the text which appears hereinbelow.

Special Technical Feature in view of Feinberg

The Examiner states that the invention has no special technical feature over the teaching in Feinberg, in view of Chaout, et al, and Toder, et al.

The examiner tells us that Feinberg teaches increased success rate of assisted reproduction by administering TGFβ, prior to, simultaneous with, or following introduction of ovum, sperm or conceptus to promote adhesiveness of trophoblast to the extracellular matrix and thereby enhance the implantation of the ovum or conceptus. The Examiner finds a difference between Feinberg and the present invention as follows:

"Feinberg et al ('825) differs from the claimed invention by not disclosing the use of the paternal antigen in the same process"

The examiner then points to Chaout and Toder who are said to teach administering paternal or third party antigens to enhance fertility, and combines them with Feinberg to arrive at the present invention. Applicants respectfully submit that Feinberg is directed to a quite distinct invention relative to the present invention, and that the present invention revolves around the capacity to elicit a "transient hyporesponsive immune reaction", which particularly distinguishes the present invention.

The Feinberg document sets out their finding most specifically in column 4 at lines 66 *et seq*.

Applicants have now found that transforming growth factor β (TGFβ), stimulates the production of trophoblast fibronectin including tropho-uteronectin.

The data of Feinberg relates to the attachment of trophoblasts to plasma fibronectin surfaces.

The instant invention sets out the present discovery at page 5 lines 25 and 26 of the present specification.

The inventors have identified TGFβ as a principal immune regulatory molecule within seminal plasma.

Additionally the inventors have shown that TGFβ, when administered to the female reproductive tract together with sperm or semen, can elicit tolerance towards male antigens, including paternal MHC class I antigens.

None of the prior art teaches that TGFβ has an immunomodulating role in fertility, and there is no suggestion that that use of TGFβ might provide for a mechanism of enhancing fertility by immunomodulation.

It is the submission of Applicants of the present invention that there are material differences in the approach to using TGFβ to immunomodulate on the one hand, and to stimulate production of fibronectin on the other hand.

The Examiner will note by reference to Massagué (enclosed) pages 617 (immunosuppression) and 610 (fibronectin production) that the activity of the fibronectin stimulation referred to is considered a quite separate sphere than the activity of an immunosuppressive activity. (Massagué, *Annu Rev Cell Biol* (1990) 6:597-641.)

The tolerance of the present invention requires considerably higher levels of TGFβ than required for induction of fibronectin set out in Feinberg. The levels referred to in column 6 lines 33 through 41 range from about 0.1 ng/ml to 5 ng/ml. The present invention envisions much higher levels for example reference is made on page 8 lines 26 through 35 ranges of total TGFβ administered as being at least an order of magnitude higher and a clinical trial currently contemplates using milligram amounts.

Similarly there is a temporal issue. The present claims are directed to exposure to TGFβ and paternal antigen before conception. The examples in Feinberg related to implantation of the conceptus in the uterus, and event that takes place some 4 days after conception. The examples in the Feinberg disclosure relate specifically to the in vitro exposure just prior to implantation, to elicit the formation of a form of fibronectin that is found to be important in implantation. TGFβ is however cleared within a few minutes *in vivo* (Wakefield et al 1991 *J Clin Invest,* 86; 1976-84, enclosed). Thus TGFβ would not be present in the uterine cavity even if administered at the time of conception, let alone in the time frame of 2 weeks prior to assessment as set out in examples 3 and 4 of the present specification. Accordingly the administration of TGFβ before conception as claimed in the present invention would not be capable of enhancing implantation by inducing fibronectin induction as at the time of implantation as taught by Feinberg.

It is for these reasons that we say that Feinberg has not taught the present invention, and has not specifically taught the induction of a hypoimmune response, and the conditions set out by Feinberg would not lead to a hypoimmune response, even if combined with Chaout and Toder.

Indeed because Feinberg does not show, or even suggest immunomodulation by use of TGFβ there is no reason to believe that combination of Feinberg with Chaout and Toder would lead to an enhancement, and therefore there is no motivation to combine the documents.

Accordingly, it is the Applicants' submission that there is unity of invention and all claims should be examined, and at least all of claims 51 through 93.

Unity of invention of the three isoforms of TGFβ - 1, 2, and 3.

The Examiner's position is stated as being that each one of the TGFβ isoforms should be considered a separate invention because "a person of ordinary skill in the art would not envision one in view of the other". The inventors believe, on the contrary, that all three classes of TGFβ would in fact be considered as the same invention and that the use of two remaining isoforms of TGFβ would be obvious in view of the use of the first.

Firstly, the different isoforms of TGFβ are not recognised as necessarily having a distinct biological function. Quite the contrary, the isoforms are recognised generally as having similar biological activity, but at times the action is different. The difference can be the result of having the same effect at different concentration, or by reason of being expressed in different tissue types, and in other instances it appears that the effect is quite different. (see, p. 602 Massagué, *Annu Rev Cell Biol* (1990) 6:597-641.)

Massagué pp608.

> Most of the current information on the activity of TGFβ derives from the study of TGFβ 1, 2 and 3. As mentioned above these TGFβ 1 isoforms acting on cultured cells often display similar activity and potency, but occasionally show marked differences. . . .

One of the reasons for the common activity is that the three mammalian isoforms of TGFβ all signal through the same serine-threonine kinase receptors. With specific regard to the immunomodulation aspect of TGFβ we refer to Massagué pp617 wherein both TGFβ 1 and

TGFβ 2 are said to potentially having immunosuppressive activities. Presumably the effect of TGFβ 3 in that regard had not yet been reported.

A later publication by Schiött *et al* (1998, *Scan J Immunol* 48, 371-378, enclosed) also refers to commonality of action in relation to an immunological response by the three isoforms TGFβ 1, 2 and 3.

Given that the present invention is largely concerned with an immunosuppressive effect, it is Applicants' submission that the person skilled in the art could quite readily conceive that all of TGFβ 1, -2, -3 would act in the same way. It is our submission that on discovery that one isoform of TGFβ acts to enhance fertility by immunomodulation, it would, in view of all three isoforms having immunomodulating activity, be obvious to try the other isotypes, with a high expectation that they might work. Given the large amount of common activity of the different isotypes of TGFβ, it is hard to imagine that it is non-obvious on finding that one isoform has an effect, that other isoforms also have an effect.

Indeed that is exactly what the present inventors have done. The patent has data comparing the immunomodulating activity of TGFβ 1 and TGFβ 2 and since filing the patent it has been found that all three forms of TGFβ have the capacity to elicit an increase in GM-CSF production in the cervix and with similar potency. We enclose a figure showing that data.

We also refer the Examiner to the Feinberg citation wherein claims were granted to all isoforms of TGFβ notwithstanding that Feinberg appears (column 9 line 66) to have data only in relation to TGFβ1. The examiner will note that the five isoforms of TGFβ were well known before Feinberg was filed. We refer to Massagué pp 601 indicating that TGFβ3 and TGFβ4 were identified in 1988, TGFβ5 was identified in 1990, the filing date of Feinberg is March 10, 1993.

Unity of invention active versus precursor forms of TGFβ

It is known that TGFβ can take the form of a latent precursor. Activation is via extreme pH (<4 or >9), chaotropic agents, or plasmin *in vitro* (see pp 604 Massagué). The vaginal tract has a pH low enough to activate TGFβ and thus it is immaterial to the end effect whether an active or precursor form of TGFβ be administered. Chu, et al (1996) *Fertility and Sterility* vol 66(2); 327-330 and Nocera and Chu (1995) *American Journal of Reproductive Immunology* vol 33(4) 282-291, documents cited in the International Search Report, both disclose that seminal fluid contains a high concentration of TGFβ and that is predominantly in the inactive form. The acidic environment of the vaginal tract is suggested by those authors as likely to activate TGFβ. Which supports the inventor's position that applying either latent or active forms to the cervix will provide the same result.

Thus, once activated, the precursor TGFβ will have precisely the same activity as if the active form were to be supplied. Active TGFβ has a quite short half life as it is normally cleared within minutes. Thus, it might be expected that supply of precursor form may well provide benefits in so far as providing some delay in release, however, it is well known to provide for slow release matrices or gels, that afford protection of labile molecules, and therefore supply of an active TGFβ would be quite as acceptable as supplying precursor TGFβ.

It is respectfully submitted that to restrict a patent to simply either active or inactive form of TGFβ is unduly restrictive because an obvious variation would avoid the patent claim. Secondly, the invention is submitted to be the same invention because the underlying novelty is the same, i.e., the finding that conception can be enhanced by administering TGFβ and a paternal antigen.

Applicants respectfully submit that *all* of the claims of the present application are sufficiently narrow to allow the Examiner to determine patentability without being subjected to a serious burden during examination. Consequently, Applicants respectfully request that the Examiner withdraw the restriction requirement altogether.

In the alternative, however, Applicants request that the Examiner give careful consideration to their proposal to examine the inventions set forth in claims 53-91 or alternatively, the inventions set forth in Groups I-XXX, for the reasons which have set forth in great detail hereinabove.

Finally, should the Examiner not be prepared to accept any of the above submissions, or either of the alternative groupings, Applicants respectfully request that claims 68 and 69 *at least* be included in the examination along with the elected invention. Claims 68 and 69 refer to levels of TGFβ to be used in the treatment and should be included along with the elected invention. It is difficult to understand the exclusion of claims 68-69, especially if claims to the patent are ultimately restricted to the use of a sperm antigen and active TGFβ2. Applicants, therefore, fail to see how the claims to be examined might not also properly include a definition of the levels as provided in claims 68-69, and consideration of such inclusion is respectfully requested..

The Examiner is respectfully requested to call the undersigned attorney at the number set forth below, should there be a need to discuss this restriction requirement and Applicants proposed election of the claims of Group XII, or alternative groupings.

Dated: 12/26/00

Respectfully submitted,

Coleman Sudol, LLP

By: _____
Henry D. Coleman
Reg. No. 32,559
708 Third Avenue, 14th Floor
New York, New York 10017-4101
(212) 679-0090

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C., 20231, on December 26, 2000.

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Henry D. Coleman (Reg. No. 32,559)